## REMARKS

### I. The Outstanding Rejections

The Examiner withdrew a number of the previous rejections. In addition, the Examiner maintained, and in some cases elaborated upon the following rejections. The current rejections are set out below.

Claims 78, 109, 140, 171 and 202 stand rejected under 35 U.S.C. 112 as failing to comply with the written description requirement with respect to the adenoviral composition being "essentially free of BSA."

Claims 70-78 and 80-100 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Zhang et al. US 6,410,010 as further evidenced by Huyghe et al., Human Gene Therapy 6:1403-1416 (1995), and further in view of Perrin et al., (1995) Vaccine, 13(13): 1244-50.

Claim 74 stands rejected under 35 U.S.C. § 103(a) Zhang et al. US 6,410,010 as further evidenced by Huyghe et al., Human Gene Therapy 6:1403-1416 (1995) and Nadeau et al., (1996) Biotechnology and Bioengineering, 51:613-623, or Trepanier et al., (1981) J. Virological Methods, 3: 201-1 in further view of Perrin et al., Vaccine 13(13):1244-50 (1995).

Claims 101, 102-105 and 106-131 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Zhang et al. US 6,410,010 as further evidenced by Huyghe et al. , Human Gene Therapy 6:1403-1416 (1995) further in view of Perrin et al., Vaccine, 13(13): 1244-50 (1995).

Claims 132, 133-136 and 137-162 stand rejected under 35 U.S.C. § 103(a) over Zhang et al. US 6,410,010 as further evidenced by Huyghe et al., Human Gene Therapy 6:1403-1416 (1995) and Perrin et al., Vaccine, 13(13): 1244-50 (1995).

Claim 105 stands rejected under 35 U.S.C. 103(a) over Zhang et al. US 6,410,010 as further evidenced by Huyghe et al., Human Gene Therapy 6:1403-1416 (1995) and further in view of Perrin et al., Vaccine, 13(13): 1244-50 (1995) and in view of Nadeau et al., Biotechnology and Bioengineering, 51:613-623 (1996) or Trepanier et al., J. Virol. Meth. 3:201-211 (1981).

Claims 163-193 stand rejected 35 U.S.C. §103(a) over Zhang et al. as further evidenced by Huyghe et al., Human Gene Therapy 6:1403-1416 (1995) and Graham et al., in further view of Perrin, Vaccine, 13(13): 1244-50 (1995).

Claim 167 stands rejected under 35 U.S.C. § 103(a) over Zhang et al. US 6,410,010 as further evidenced by Huyghe et al., Human Gene Therapy 6:1403-1416 (1995) and in view of Graham et al., or as further in light of Perrin, Vaccine, 13(13): 1244-50 (1995) and further in view of Nadeau et al., Biotechnology and Bioengineering, 51:613-623 (1996) or Trepanier et al., J. Virol. Meth. 3:201-211 (1981).

Claims 194-226 stand rejected under 35 U.S.C. § 103(a) over Zhang et al. US 6,410,010 and Huyghe et al., Human Gene Therapy 6:1403-1416 (1995) as further evidenced by Huyghe and further in view of Perrin et al., Vaccine, 13(13): 1244-50 (1995).

Claim 198 stands rejected under 35 U.S.C. § 103(a) over Zhang et al. US 6,410,010 and Huyghe et al., Human Gene Therapy 6:1403-1416 (1995) as further evidenced by Perrin, Vaccine, 13(13): 1244-50 (1995) and further in view of Nadeau et al., Biotechnology and Bioengineering, 51:613-623 (1996) or Trepanier et al., J. Virol. Meth. 3:201-211 (1981).

## II. Patentability Arguments

Applicants' invention is directed to improved methods of treating patients with therapeutic adenovirus compositions comprising: a) preparing a therapeutic adenovirus composition by methods including steps of growing host cells in a media, providing nutrients to those cells, infecting the host cells with an adenovirus, lysing the host cells to provide a lysate and purifying the lysate; and b) administering the therapeutic adenovirus composition to a patient.

The art of large scale virus production in host cells for use as vectors in gene therapy has been faced with several challenges in recent years. First, there has existed a desire to eliminate bovine serum proteins in cell culture media because of outbreaks of Bovine Spongiform Encephalopathy (BSE) throughout the world. Further, there has existed a desire to use suspension cells for adenoviral vector production because of the existing limitations on the scalability of microcarrier cultures to produce large quantities of adenoviral vectors for gene therapy.

Unfortunately, where adenoviral cultures have been adapted to be serum-free suspension cultures, the cell-specific virus yields in the adapted suspension cells are about 5-10-fold lower than those achieved in the parental attached cells. Accordingly, there have existed no reports on the use of 293 suspension cells for adenoviral vector production for gene therapy until Applicants' invention.

As one aspect of their invention, Applicants have successfully adapted 293A (attached) cells into serum-free suspension culture (293SF cells) which are particularly useful for the large-scale production of growing cells on serum free media. The development of this serum-free 293 suspension culture was deemed to be a major process improvement for the production of adenoviral vectors for gene therapy. The methods of the invention are particularly useful for providing highly purified adenovirus compositions characterized by low levels of contaminant nucleic acids and/or serum proteins.

Applicants claim various aspects of their invention in various ways but their claims are both supported by their disclosure and define subject matter which is unobvious over the prior art.

A. The Disclosure Provides Implicit Support for the Recitation of "essentially free of BSA" and the New Matter/Lack of Written Description Rejection Under 35 U.S.C. §112 (first paragraph) Should be Withdrawn.

The new matter/lack of written description rejection of claims 78, 109, 140, 171 and 202 under 35 U.S.C. §112 (first paragraph) on the basis that the claim recitation that the therapeutic adenovirus composition is "essentially free of BSA" should be withdrawn because Applicants' specification conveys with reasonable clarity to those skilled in the art that, as of the filling date sought, they were in possession of the invention as now claimed. See Vac-Cath, Inc. v. Mahurkar,19 U.S.P.Q. 2d 1111 at 1117 (Fed. Cir. 1983).

Applicants submit that the Examiner's finding of "implicit support for such limitation" in the form of the method of Example 6 (Office Action at page 4, line 1-6) supports the language of their claim. The test for written description is whether the disclosure reasonable conveys to the worker of ordinary skill in the art that the inventors, at the time their application was filed, had possession of their claimed invention and an *ipsis verbis* disclosure is not necessary to satisfy the written description requirement. See In re Edwards, 196 U.S.P.Q. 465, 467 (CCPA 1978). Support for such claim language can be either implicit or explicit.

The skilled artisan reading the disclosure is instructed that one aspect of the invention is directed to the removal of contaminating proteins and viruses from the purified products of the invention. In particular, concerns over the outbreak of Bovine Spongiform Encephalopathy (BSE) ("mad cow disease") transmitted by infectious agents comprising

abnormally structured bovine proteins (prions) dictates a particular concern with the removal of serum proteins. Thus, the specification teaches:

> "Historically, presence of bovine source proteins in cell culture media has been a regulatory concerns, especially recently because of the outbreak of Bovine Spongiform Encephalopathy (BSE) in some countries. Rigorous and complex downstream purification process has to be developed to remove contaminating proteins and any adventitious viruses from the final product. Development of serum-free 293 suspension culture is deemed to be a major process improvement for the production of adenoviral vector for gene therapy." (page 28, lines 11-17)

In order to accomplish this goal the specification teaches the adaptation of cells for growth in "serum-free" media .... "More particularly, the serum-free media comprises a fetal bovine serum content of less than 0.03% v/v." (page 7, lines 5-9) The resulting adenoviral product "should be **essentially free** of pyrogens, as well as other impurities that could be harmful to humans or animals." (emphasis supplied, page 72, lines 15-17)

The specification also makes it clear to the reader that significant reduction in BSA content of the purified adenoviral product was a particularly important goal. For example, the specification states that "[a]s shown in FIG. 12, all the major adenovirus structure proteins are detected on the SDS-PAGE. The IEC purified virus shows equivalent staining as that of the double CsCl purified virus. Significant reduction in bovine serum albumin (BSA) concentration was achieved during purification. The BSA concentration in the purified virus was below the detection level of the western blot assay as shown in FIG. 13." Specification, page 92, , lines 4-8 [para. 0337]. And later, the specification notes that "[t]he purified virus was further analyzed by SDS-PAGE, western blot for BSA, and nucleic acid slot blot to determine the contaminating nucleic acid concentration. The analysis results are given in FIG. 19A, FIG. 19B and FIG. 19C, respectively." Page 96, lines 22-24 [para. 0352]. There can be no question but that reductions, and even removal entirely, of BSA was a principal goal of the inventors, a goal that was shown to have been achieved.

Taken together, these teachings that (1) bovine proteins constitute a significant and dangerous contaminant which should be removed from the therapeutic compositions; (2) the instruction that the compositions "should be essentially free of pyrogens, as well as other impurities..."; and (3) the demonstration that BSA could not be detected in the purified

composition constitute an explicit disclosure that the Applicants were in possession of the invention of compositions "essentially free of BSA" as of their filing date.

For these reasons, the new matter/lack of written description rejection should be withdrawn.

B. The Section 103 Rejections Should be Withdrawn Because there is no Prima Facie Case of Obviousness.

Applicants' claims are all (except claims 103, 104, 196 and 197)[1] directed to the culturing of adenovirus under serum-free conditions (claims 70-100, 110, 141, 172 and 203) and/or recite formulation of a therapeutic adenovirus composition with "a BSA content below the detection limit of a western blot assay" or "essentially free of BSA" (claims 78, 101, 102, 105-195 and 198 -226).

All of the prior art rejections (except that of dependent claim 167 as will be discussed below) are based upon the combination of Zhang with Huyghe and Perrin together or further in combination with additional references such as Graham (claims 163-193) or with other references such as Trepanier (claims 74, 105, 167 and 198) and, Nadeau (claims 74, 105, 167 and 198). The necessity for the Perrin disclosure is significant because all the rejections of Applicants' adenovirus treatment claims (except one rejection of claim 167) rely upon Perrin as disclosing the element missing from the other references of: 1) the use of a serum-free media, 2) BSA levels below the detection limit of western blots or essentially free of BSA, or 3) the use of a bioreactor or microcarrier.

Perrin is not applicable to the present invention because it bears no relation or relevance to the production of adenovirus. Instead Perrin relates only to rabies virus production – a totally distinct virus that is produced in different cells under different conditions! Accordingly, there is no prima facie case of obviousness because no evidence has been presented that the disclosure of rabies virus reference (Perrin) is combinable with those of the adenovirus references. On the contrary, Applicants have presented evidence, in the form of the Zhang Declaration, that, due to their substantial structural and biological

[1] Remaining claims 103 and 104 are directed to methods comprising the step of "growing host cells in a bioreactor or on a microcarrier" while claims 196 and 197 are directed to providing nutrients to host cells "by perfusion or roller bottle process."

differences, those of skill in the art would ***not*** in any way equate rabies virus and rabies virus production with adenovirus so combine the references.

Not only does Perrin utilize a different cell-type (BHK-21 cells) than do the adenovirus references or Applicants (293 cells), but there is no instruction that one could successfully carry out viral production methods in culture other cell types, much less 293 cells, in the absence of serum. For example, Perrin at page 1249, col. 1, first para. discloses that the absence of serum affected the BHK-21 cells by "modify[ing] their sensitivity to rabies virus or had selected apparently less sensitive cells." From this passage, it is evident that the absence of serum had an adverse effect on the BVHK-21 cells, resulting in a loss of sensitivity to rabies virus infection. Who knows what such a treatment would have done to cell lines used for adenovirus production? At the very least, this passage evidences that there is a high degree of uncertainty surrounding the effects of serum removal and the continuing ability of cells to remain receptive to infection by adenovirus – or any virus for that matter! While Perrin states that they were able to solve the problem in the case of rabies virus, the fact remains that the ability to solve such problems in the case of a virus, such as adenovirus, having an entirely different infection process is clearly uncertain.

In hindsight, it is now known that the 293 host cells can grow adenovirus under serum-free conditions but there was no teaching in the art relied on by the Examiner that one would be successful in doing so prior to Applicants' own disclosure.

1. The 35 U.S.C. §103 rejections of claims 70-100, 110, 141, 172 and 203 based on the combination of references teaching adenovirus production on serum-containing media with a single reference (Perrin) teaching rabies virus production on serum-free media should be withdrawn.

The art-based rejections of claims 70-100, 110, 141, 172 and 203 directed to adenovirus production using serum-free media should be withdrawn because all the references directed to culturing adenovirus (Zhang, Huyghe, Graham, and Nadeau) teach the use of serum-containing media while the one reference utilizing serum-free media (Perrin) is directed to the culturing of a rabies virus and not adenovirus.

Not only is there no motivation in the art to combine the teachings of the disparate references, but Perrin itself teaches away from any general application of its method to other viruses when it notes that:

> "Several SFM [serum-free media] have been developed and are currently used for the production of monoclonal antibodies or recombinant proteins, but not for the production of classical viral vaccines." (emphasis supplied, page, 1245, col. 1, lines 2-4)

Accordingly, there would have been no expectation that the elements from the two groups of references could be successfully combined to yield a successful serum-free adenoviral production method.

As noted in the Examiner's withdrawal of the anticipation and obviousness rejections over Zhang and Huyghe alone (see page 7, lines 3-4 or the Office Action dated August 8, 2006) those references neither disclose nor suggest the use of serum-free media for the production of adenovirus. Specifically, Zhang discloses the culture of adenovirus producing 293 cells in MEM with horse sera. Huyghe cultures adenovirus producing 293 cells in a medium supplemented with fetal bovine serum (FBS). Graham cultures 293 cells in media with fetal bovine serum (FBS). Trepanier cultures HEp-2 cells in media with fetal bovine serum (FBS) to produce Human respiratory syncytial virus, and Nadeau cultures 293 cells with either bovine serum or newborn calf serum. None of these references teach or suggest the use of a serum-free media.

In contrast to all of the cited references teaching adenovirus production using serum-based media, Perrin is directed to a method of culturing rabies virus which is substantially different from and non-analogous to culturing adenovirus. Specifically, rabies virus is an enveloped "budding" RNA-based rhabdovirus whereas adenovirus, as in the instant invention, is a DNA capsid based non-enveloped virus of an entirely different viral family. The viruses therefore replicate differently and grow differently See Zhang Declaration para. 14. As such, one of ordinary skill in the art would not and could not have predicted that the successful use of serum-free media in a rabies virus culture would also be successful in an adenovirus culture.

Furthermore, a *prima facie* case of obviousness requires that there be a reasonable expectation of success of practicing the claimed invention based on the combination of references. That expectation is lacking in the present case because of the distinctions between a rabies virus and adenovirus. Thus, Perrin would not have been expected to address the hurdle facing the combination of the Zhang, Huyghe, Nadeau, Trepanier and Graham

references because the rabies virus is quite distinct in its structure and biological properties from adenovirus.

The Examiner erred in disputing the relevancy of the Declaration of Shuyuan Zhang Under 37 C.F.R. §1.132[2], in asserting that it failed to provide scientific or logical reasoning why the successful culturing of rabies virus on a serum-free media would not be expected to succeed in the culturing of adenovirus. Specifically, the Zhang Declaration asserted several reasons why a rabies virus culturing system would not necessarily be expected to be useful in the culturing of adenovirus. In particular, the Declaration described the different structures of rabies and adenoviruses (one is DNA-based, the other RNA-based) and further stated that rabies virus and adenovirus "infect and grow differently and replicate differently." Based upon these differences (which have not been disputed by the Examiner) Zhang concluded that "there is no *a priori* expectation that propagation of rabies viruses would provide appropriate means for adenovirus preparations."

In addition, the Examiner's reasons why Perrin "would be combined with the other references" are unsupported and conclusory.

> "The Artisan would have been motivated to do so [combine Zhang with the steps of Perrin] because such methods were standard in the art. Moreover, the Artisan would have had reasonable expectation of success, as the art had already demonstrated that such methods are successful in producing virus." (Official Action of 12/16/05, p 20, paragraph 4, emphasis supplied)

With the exception of the Perrin rabies virus reference (and indeed contrary to Perrin's express teachings), the Examiner failed to establish that serum-free methods were "standard in the art" generally and failed to make any showing of the use of serum-free methods in the adenovirus art specifically. Moreover, the only "successful" use of such serum-free methods "in producing virus" cited by the Examiner was with the rabies virus. Applicants' own success with adenovirus cannot be used against them in hindsight. Finally, the Examiner improperly simplified the issues facing the worker in the art when he argued at page 8 of the August 8, 2006 Office Action that:

[2] Filed March 8, 2004 in co-owned and copending U.S. Serial No. 09/203,078 and submitted in this application on June 8, 2006.

> "Perrin provides an art accepted methodology for removing contaminants, such as BSA, in the preparation of culture based pharmaceutical compositions. Perrin is not relied upon for solving any problem in culturing adenovirus, per se, rather it is relied on simply to demonstrate that there were art accepted methods for culturing to remove BSA from viral based pharmaceutical compositions."

The issue was not whether it would have been desirable to reduce BSA in viral based pharmaceutical compositions by culturing the host cells in the absence of serum. Neither was the issue whether any virus compositions could be produced in the absence of serum. Instead, the issue was whether doing so could be effectively accomplished for adenoviral based compositions.

As discussed previously, Perrin is not applicable to the present invention because it bears no relation or relevance to the production of adenovirus. Instead Perrin relates only to rabies virus production – a totally distinct virus that is produced in different cells under different conditions! Accordingly, there is no prima facie case of obviousness because no evidence has been presented that the disclosure of rabies virus reference (Perrin) is combinable with those of the adenovirus references. On the contrary, Applicants have presented evidence, in the form of the Zhang Declaration, that, due to their substantial structural and biological differences, those of skill in the art would ***not*** in any way equate rabies virus and rabies virus production with adenovirus so combine the references.

Not only does Perrin utilize a different cell-type (BHK-21 cells) than do the adenovirus references or Applicants (293 cells), but there is no instruction that one could successfully carry out viral production methods in culture other cell types, much less 293 cells, in the absence of serum. For example, Perrin at page 1249, col. 1, first para. discloses that the absence of serum affected the BHK-21 cells by "modify[ing] their sensitivity to rabies virus or had selected apparently less sensitive cells." From this passage, it is evident that the absence of serum had an adverse effect on the BVHK-21 cells, resulting in a loss of sensitivity to rabies virus infection. Who knows what such a treatment would have done to cell lines used for adenovirus production? At the very least, this passage evidences that there is a high degree of uncertainty surrounding the effects of serum removal and the continuing ability of cells to remain receptive to infection by adenovirus – or any virus for that matter! While Perrin states that they were able to solve the problem in the case of rabies virus, the

fact remains that the ability to solve such problems in the case of a virus, such as adenovirus, having an entirely different infection process is clearly uncertain.

The Section 103 rejections of claims 70-100, 110, 141, 172 and 203 should be withdrawn because the Examiner has failed to cite evidence that those of ordinary skill would have reasonably expected that adenoviral production methods could be carried out in serum-free media.

2. The 35 U.S.C. §103 rejections of claims 70, 71, 74-102, 105-195 and 198-226 based on the combination of references teaching adenovirus production on serum-containing media with a single reference (Perrin) teaching rabies virus production on serum-free media should be withdrawn.

The art-based rejections of claims 70, 71, 74-102, 105-195 and 226 based on combinations of adenovirus art (Zhang, Huyghe, Graham, and Nadeau) with Perrin as showing serum-free rabies virus production to produce a BSA-free adenovirus composition should be withdrawn because there is no instruction to combine the Perrin rabies disclosure with the adenovirus references. Moreover, the cited references evidence no expectation that successful serum-free production of adenovirus could be carried out to produce a therapeutic adenovirus composition that was "essentially free of BSA" (claims 78, 109, 140, 171 and 202) or had "a BSA content below the detection level of a western blot assay" (claims 70, 71, 74-102, 105-195).

Not only is there no motivation in the art to combine the teachings of the disparate references, but Perrin itself teaches away from any general application of its method to other viruses when it notes that:

> "Several SFM [serum-free media] have been developed and are currently used for the production of monoclonal antibodies or recombinant proteins, but not for the production of classical viral vaccines." (emphasis supplied, page, 1245, col. 1, lines 2-4)

Accordingly, there would have been no expectation that the elements from the two groups of references could be successfully combined to yield a successful serum-free adenoviral production method.

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In contrast to these cited references teaching adenovirus production using serum-based media, Perrin is directed to a method of culturing rabies virus which is substantially different from and non-analogous to culturing adenovirus. Specifically, rabies virus is an enveloped "budding" RNA-based rhabdovirus whereas adenovirus, as in the instant invention, is a DNA capsid based non-enveloped virus of an entirely different viral family. The viruses therefore replicate differently and grow differently. As such, one of ordinary skill in the art would not and could not have predicted that the successful use of serum-free media in a rabies virus culture would also be successful in an adenovirus culture.

Furthermore, a *prima facie* case of obviousness requires that there be a reasonable expectation of success of practicing the claimed invention based on the combination of references. In the present case, that expectation is lacking because of the distinctions between a rabies virus and adenovirus. Thus, Perrin would not have been expected to address the hurdle facing the combination of the Zhang, Huyghe, Nadeau, Trepanier and Graham references because the rabies virus is quite distinct in its structure and biological properties from adenovirus.

The Examiner erred in disputing the relevancy of the Declaration of Shuyuan Zhang Under 37 C.F.R. §1.132 in asserting that it failed to provide scientific or logical reasoning why the successful culturing of rabies virus on a serum-free media would not be expected to succeed in the culturing of adenovirus. Specifically, the Zhang Declaration asserted several reasons why a rabies virus culturing system would not necessarily be expected to be useful in the culturing of adenovirus. In particular, the Declaration described the different structures of rabies and adenoviruses (one is DNA-based, the other RNA-based) and further stated that rabies virus and adenovirus "infect and grow differently and replicate differently." Based

upon these differences (which have not been disputed by the Examiner) Zhang concluded that "there is no *a priori* expectation that propagation of rabies viruses would provide appropriate means for adenovirus preparations."

In addition, the Examiner's reasons why Perrin "would be combined with the other references (Official Action of 12/16/05, p 20, paragraph 4) are unsupported and conclusory.

> "The Artisan would have been motivated to do so [combine Zhang with the steps of Perrin] because such methods were standard in the art. Moreover, the Artisan would have had reasonable expectation of success, as the art had already demonstrated that such methods are successful in producing virus." (emphasis supplied)

With the exception of the Perrin rabies virus reference (and indeed contrary to Perrin's express teachings), the Examiner failed to establish that serum-free methods were "standard in the art" generally and failed to make any showing of the use of serum-free methods in the adenovirus art specifically. Moreover, the only "successful" use of such serum-free methods "in producing virus" cited by the Examiner was with the rabies virus. Applicants' own success with adenovirus cannot be used against them in hindsight. Finally, the Examiner improperly simplified the issues facing the worker in the art when he argued at page 8 of the August 8, 2006 Office Action that:

> "Perrin provides an art accepted methodology for removing contaminants, such as BSA, in the preparation of culture based pharmaceutical compositions. Perrin is not relied upon for solving any problem in culturing adenovirus, per se, rather it is relied on simply to demonstrate that there were art accepted methods for culturing to remove BSA from viral based pharmaceutical compositions."

The issue was not whether it would have been desirable to reduce BSA in viral based pharmaceutical compositions by culturing the host cells in the absence of serum. Neither was the issue whether any virus compositions could be produced in the absence of serum. Instead, the issue was whether doing so could be effectively accomplished for adenoviral based compositions. The Section 103 rejections of claims 70, 71, 74-102, 105-195 and 198-226 should be withdrawn because the Examiner has failed to cite evidence that those of ordinary skill would have reasonably expected that adenoviral production methods could be carried out in serum-free media so as to produce BSA free therapeutic compositions.

3. The 35 U.S.C. §103 rejections of claims 80, 101-131, 142, 163-193 and 204 directed to growing host cells on a bioreactor or microcarrier based on the combination of the adenovirus production references with Perrin teaching rabies virus production on serum-free media should be withdrawn.

The art-based rejections of claims 80, 101-131, 142, 163-193 and 204 directed to the production of purified adenovirus compositions by growing host cells in a bioreactor or on a microcarrier based on combinations of adenovirus art (Zhang, Huyghe, Graham, and Nadeau) with Perrin on the basis that Perrin discloses the use of a bioreactor or microcarrier should be withdrawn because there is no instruction to combine the Perrin rabies disclosure with the adenovirus references for the reasons set out in Sections 1. and 2. above.

The Examiner stated that the Zhang, Huyghe and Graham references failed to teach a bioreactor or microcarrier (Office Action of August 8, 2006 at page 14, last line and page 15, last three lines) and relies upon Perrin as disclosing that "it was standard in the art to use such bioreactors with such microcarriers." The Examiner has failed to establish the use of such bioreactors in the adenovirus art or to set out why the use of such reactors in the rabies virus art would have been obvious in the production of adenovirus compositions.

For these reasons, the rejections of claims 80, 101-131, 142, 163-193 and 204 should be withdrawn.

4. The 35 U.S.C. §103 rejections of claims 82-84, 113, 132-162, 166-193 and 194-226 directed to providing nutrients to host cells by perfusion, fed batch or automated roller bottles based on the combination of the adenovirus production references with Perrin teaching rabies virus production on serum-free media should be withdrawn.

The art-based rejections of claims 82-84, 113, 132-162, 166-193 and 194-226 directed to providing nutrients to host cells by perfusion, fed batch or automated roller bottles based on combinations of adenovirus art (Zhang, Huyghe, Graham, and Nadeau) with Perrin on the basis that Perrin discloses the use of a bioreactor or microcarrier should be withdrawn because there is no instruction to combine the Perrin rabies disclosure with the adenovirus references for the reasons set out in Sections 1. and 2. above.

The Examiner stated that the Zhang and Graham references failed to teach the use of perfusion techniques, fed batch or roller bottles and withdrew the assertion that Huyghe taught feeding the batch. (Office Action of August 8, 2006 at page 15, lines 9-21) Instead,

the Examiner relied upon Perrin for teaching those techniques. As discussed extensively in Sections 1 and 2 above, the Examiner has failed to establish why one of skill in the art would combine elements disclosed only in a rabies vaccine reference to modify the teachings of a number of adenovirus references none of which teach those elements.

The Examiner has failed to establish the use of perfusion, fed batch or roller bottle feeding methods in the adenovirus art or to set out why the use of such nutrient provision methods in the rabies virus art would have obvious in the production of adenovirus compositions. For these reasons, the rejections of each of claims 82-84, 113, 132-162, 166-193 and 194-226 should be withdrawn.

In addition, even if it is held that Huyghe or other references such as Nadeau disclose use of fed batch feeding (which assertion the Examiner withdrew) the rejections of claims 194-226 which are directed to the use of perfusion or automated roller bottle techniques should be withdrawn in light of the failure of any reference other than Perrin to teach those techniques.

a. The Rejection of Claims 82, 113, 144, 175 and 206 directed to the use of Perfusion Should be Withdrawn.

Moreover, Applicants' use of perfusion (as specifically recited in claims 82, 113, 144, 175 and 206) unexpectedly provided a cleaner and more highly purified adenovirus compositions. (Page 11, line 23 through page 12, line 10) Thus, even if the rejection of claims 82-84, 113, 132-162, 166-193 and 194-226 is not withdrawn, the rejection of claims 82, 113, 144, 175 and 206 should be.

5. The 35 U.S.C. §103 rejections of claims 101-131, 132-162 and 167 based on the combination of references teaching adenovirus production on serum-containing media with a single reference (Perrin) teaching rabies virus production in serum-free media should be withdrawn.

The art-based rejections of claims 101-226 based on the combination of one or more of (Zhang, Huyghe, Graham, Trepanier and Nadeau) with Perrin should be withdrawn for the reasons set out in Sections 1 and 2. above. Moreover, the rejections of each of claims 101-131, 132-162 and 167 should be withdrawn because Applicants have established that the products resulting from practice of their methods are different from those taught by the prior art.

Specifically, the Examiner stated that "[i]n the absence of evidence to the contrary the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences." (Office Action of August 8, 2006 at page 11) The specification itself provides evidence to the contrary by demonstrating the improvements in yields for a given purity.

One aspect of the invention relates to the need for a method which can provide adenovirus compositions with a purity comparable to double CsCl gradient purified compositions with greater throughput. Huyghe discloses a purification method which provides purity similar to that from CsCl purification but which only obtains 23% virus recovery. In contrast the method of the invention is established to provide purities down to 60 pg/ml nucleic acids (Example 6, Table 10, page 93) while the method, in one embodiment, achieves 70 ±10% virus recovery (Example 8, page 100, line 2)

6. The Section 103 Rejection of Claim 167 over the Combination of Zhang, Huyghe and Graham (in the absence of Perrin, Nadeau or Trepanier) Should be Withdrawn.

The rejection on page 16 of the Office Action of claim 167 which is only optionally based upon Perrin appears to be the only rejection not requiring Perrin as a reference. Nevertheless, independent claim 163 from which it depends and claim 167 are unobvious over the combination of Zhang, Huyghe and Graham because, as acknowledged by the Examiner, those references fail to teach serum free media, bioreactors, microcarriers or perfusion methods. Perrin is required to supply those elements in the rejection of claim 163 but the rejection of claim 167 should be withdrawn, at the very least, due to the *absence* of its citation.

Moreover, the references fail to teach the element of claim 167 wherein the therapeutic adenovirus composition has a contaminating nucleic acid concentration of less than 0.2 ng/ml. In response to the challenge that Applicants provide evidence that "the claimed products are functionally different than those taught by the prior art and to establish patentable differences" (Office Action of August 8, 2006 at page 17), the specification itself provides such evidence by showing improvements in yields for a given purity.

Specifically, the invention provides a method which can produce adenovirus compositions with a purity at least comparable to, and preferably even greater than, that of double CsCl gradient purified compositions – together with greater throughput! Huyghe

discloses a purification method which is said to provide purity similar to that from CsCl purification but which only obtains 23% virus recovery. In contrast, the method of the invention is established to provide purities down to 60 pg/ml nucleic acids (Example 6, Table 10 at page 93) while, in certain embodiments described in the disclosure the method achieves 70 ±10% virus recovery (Example 8 at page 100 line 2).

7. The 35 U.S.C. §103 rejections of claims 73, 77, 104, 108, 135, 139, 166, 170, 197 and 201 reciting a formulation having a contaminating nucleic acid concentration of less than 0.8 ng/ml should be withdrawn.

Claims 73, 77, 104, 108, 135, 139, 166, 170, 197 and 201 are separately patentable and their rejections should be withdrawn in the absence of any teaching in the art or expectation that a therapeutic adenovirus composition could be produced having a contaminating nucleic acid concentration of less than 0.8 ng/ml. While Nadeau discloses the use of ultrafiltration in a recombinant protein expression system producing protein tyrosine phosphatase (PTP1C) it teaches the use of ultrafiltration for the removal of viral particles from supernatant (page 615, col. 1, lines 8-10) not the removal of nucleic acid contaminants from adenoviral preparations.

Trepanier is not even related to adenovirus preparation but instead is directed to the concentration of human respiratory syncytial virus (HSRV) by ultrafiltration and would not be combined with the primary references directed to adenovirus. Moreover, Trepanier does not even teach the removal of contaminating nucleic acid from HSRV, much less from adenovirus which is substantially smaller (60-90 nm vs. 150-200 nm diameter) than HSRV in size. Accordingly, Trepanier would not have instructed one of ordinary skill that they could have achieved the purities of the claims.

The Examiner's hindsight observation that Applicants' method actually works to produce a product characterized by the recited contaminating nucleic acid concentrations does nothing to establish that Nadeau and Trepanier would have led one of ordinary skill in the art to believe beforehand that such results could be achieved. In the absence of some affirmative teaching of Applicants' method the rejection should be withdrawn.

8. The 35 U.S.C. §103 rejections of claims 74, 105 and 198 reciting a formulation having a contaminating nucleic acid concentration of less than 0.2 ng/ml should be withdrawn.

In addition claims 74, 105 and 198 depending from claims 73, 104 and 197 above and reciting therapeutic adenovirus compositions having a contaminating nucleic acid concentration of less than 0.2 ng/ml. are separately patentable over those claims. As was the case with a contaminant level of less than 0.8 ng/ml no actual evidence has been presented that such levels would have been expected by those skilled in the art and the rejection of those claims should be withdrawn.

## CONCLUSION

In view of the above amendments, applicants believe the pending application is in condition for allowance.

Respectfully submitted,
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